

Office Action Summary	Application No. 10/592,962	Applicant(s) SIDRANSKY, DAVID	
	Examiner JEANINE A. GOLDBERG	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11/21/11.
- 2a) ☒ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,5-7,10,11,13,15,16,37-39,44,45,51,52,54,58-63 and 69-73 is/are pending in the application.
- 4a) Of the above claim(s) 5,6,10,11,60,62,63,69 and 71-73 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,7,13,15,16,37-39,44,45,51,52,54,58,59,61 and 70 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. <u>11/11</u> . |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____. | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

1. This action is in response to the papers filed November 21, 2011. Currently, claims 1,2,5-7,10,11,13,15,16, 37-39,44,45,51,52,54,58-63 and 69-73 are pending. Claims 5,6,10,11,60,62,63,69 and 71-73 have been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

2. Applicant's election without traverse of Group I and Adenomatous polyposis coli (APC), Claims 1-2, 7, 13, 15, 16, 18, 37-39, 44-45, 51-52, 54, 58-59, 61, 70, in the paper filed January 20, 2011 is acknowledged.

The requirement is still deemed proper and is therefore made FINAL.

The response filed September 14, 2011 and November 21, 2011 have added two new required promoters to the claimed invention. Upon further review and consideration, in view of the art already of record, the amendment to the combination of GSTP1, APC, RASASF1A and CRBP1 has been entered and examined as not an additional burden in this case.

Priority

3. This application is a 371 of PCT/US05/08849, filed March 17, 2005 and claims priority 60/553,993, filed March 17, 2004.

The Bib data sheet seems to also include to 60/553,994, filed March 17, 2004, however the ADS sheet does not include the '994 application. Thus, no priority appears to be drawn to 60/553,994, filed March 17, 2004. The Bib data sheet will be fixed.

Drawings

4. The drawings are acceptable.

Information Disclosure Statement

5. The listing of references in the specification (pages 42-43) is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

Art Unit: 1634

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 1, 13, 15-16, 37-39, 44-45, 54, 61, 70 under 35 U.S.C. 103(a) as being unpatentable over Yegnasubramanian et al. (Cancer Research, Vol. 64, pages 1975-1986, March 2004) in view of Esteller et al. (Cancer Research, Vol. 62, pages 5902-5905, October 14, 2002).

Yegnasubramanian et al teaches hypermethylation of CpG Islands in primary and metastatic human prostate cancer. Yegnasubramanian teaches quantifying the promoter methylation from GSTP1 and APC in prostate cancers (abstract)(limitations of Claims 1, 2, 7, 18, 61, 70). Yegnasubramanian teaches that bisulfite modification of DNA samples and quantitative real-time methylation specific PCR (RT-MSP) were used to ascertain the amount of converted input templates in each sample (page 1976, col. 2, Figure 1)(limitations of Claim 15, 16). Yegnasubramanian teaches benign prostates were obtained and analyzed (page 1976, col. 2). Yegnasubramanian also teaches WBC DNA was taken from the WBCs of healthy volunteers (Figure 1)(limitations of Claim 13). Table 2 provides primers for each gene analyzed including GSTP1 and APC. The promoter methylation was quantitated with real-time methylation specific PCR (RT-PCR)(page 1976, col. 2)(limitations of Claim 15-16). In particular Yegnasubramanian teaches **GSTP1, APC, RASSF1alpha**, PTGS2 and MDR1 were hypermethylated in >85% of prostate cancers but not in normal prostate cancers and tissues. Yegnasubramanian further teaches that using the markers in combination

Art Unit: 1634

provided even more diagnostic power than using a single marker alone (page 1979, col. 2). Table 3 illustrates the sensitivity, specificity for each gene and several combinations of genes. All of these combinations include both GSTP1 and APC (page 1980). With respect to prognosis, Yegnasubramanian further states that the CpG islands that were frequently methylated in the primary cancers were also frequently methylated in the metastatic specimens (page 1984)(limitations of Claim 37-39, 44).

Yegnasubramanian does not specifically teach quantifying promoter methylation of CRBP1.

However, Esteller teaches primers for detection of CRBP1 methylation in normal and cancer cell lines. CRBP1 methylation appeared in premalignant lesions and frequently occurred with RARB2 methylation in the same tumors. Esteller teaches that promoter hypermethylation was found in numerous human primary tumors. Table 1 outlines numerous primary tumors that have methylation of CRBP1 promoter.

Therefore, it would have been prima facie obvious at the time the invention was made to have analyzed the promoter methylation of GSTP1, APC, RASSF1A and CRBP1 to analyze a range of cancers. The prior art teaches that GSTP1, APC, RASSF1a are hypermethylated in prostate cancers as taught by Yegnasbramanian while CRBP1 is hypermethylated in numerous cancers. Yegnasubramanian teaches that using the markers in combination provided even more diagnostic power than using a single marker alone (page 1979, col. 2). Thus, a method for combining the panel of genes taught by Yegnasbramanian and Esteller to detecting a neoplasia by detecting the hypermethylation of the promoters of GSTP1, APC, RASSF1A and CRBP1 would

Art Unit: 1634

have provided additional information and increased the information derived from the analysis to indicate the presence of a neoplasia in the sample.

7. Claims 2, 7, 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yegnasubramanian et al. (Cancer Research, Vol. 64, pages 1975-1986, March 2004) in view of Esteller et al. (Cancer Research, Vol. 62, pages 5902-5905, October 14, 2002) and further in view of Nakayama et al. (Lab Investigation, Vol. 81, No. 7, pages 1049-1057, 2001).

Yegnasubramanian and Esteller do not specifically teach analysis of promoter methylation for RARB2. Moreover, the combination of Yegnasubramanian and Esteller do not specifically teach detecting prostate cancer.

However, Nakayama teaches aberrant methylation of **RARB2** was detected in 79% of primary prostate cancers and not in normal prostate samples. Nakayama teaches using bisulfite PCR method to detail the methylation status of the RARB2 promoter region status. Table 1 illustrates that RARB2 methylation was found in normal prostate cancer and hormone-refractory prostate cancer (page 1052).

Therefore, it would have been prima facie obvious at the time the invention was made to have analyzed the promoter methylation of GSTP1, APC, RASSF1A, RARB2 and CRBP1 to detect prostate cancer. The prior art specifically teaches GSTP1, APC, RASSF1A, and RARB2 are hypermethylated in prostate cancers. The prior art further teaches that the methylation of **RAR-beta2** and **CRBP1** occurred frequently in the same tumors. CRBP1 methylation appeared in premalignant lesions and frequently occurred

Art Unit: 1634

with RARB2 methylation in the same tumors. Esteller teaches that promoter hypermethylation was found in numerous human primary tumors. It would have been prima facie obvious to have analyzed the panel of genes known to be hypermethylated in cancers to provide a better analysis of promoter methylation and detection of cancers.

With specific respect to Claims drawn to prostate cancer, the prior art teaches GSTP1, APC, RASSF1A, and RARB2 are hypermethylated in prostate cancers. The prior art further teaches that the methylation of **RAR-beta2** and **CRBP1** occurred frequently in the same tumors. It would have been prima facie obvious to analyze whether CRBP1 is hypermethylated in prostate cancers. The prior art teaches that the two genes are frequently methylated in the same tumors so there is a reasonable expectation of success that **CRBP1** is hypermethylated in prostate cancers, since RAR-beta2 promoter methylation is known to be associated with prostate cancer.

8. Claims 1, 13, 15-16, 37-39, 44-45, 54, 61, 70 70 under 35 U.S.C. 103(a) as being unpatentable over Maruyama et al. (Clinical Cancer Research, Vol. 8, pages 514-519, February 2002) in view of Esteller et al. (Cancer Research, Vol. 62, pages 5902-5905, October 14, 2002).

Maruyama teaches analyzing aberrant promoter methylation profiles of prostate cancers. In particular gene promoter methylation was analyzed in 101 prostate cancer samples (limitations of Claim 7). Among the genes analyzed were GSTP1 and APC

Art Unit: 1634

(abstract)(limitations of Claim 18). Maruyama teaches analyzing prostate specimens using MSP assays (limitations of Claim 51). Maruyama teaches that negative control samples without DNA were included for each set of PCR. Moreover, the conditions for MSP were selected to distinguish between tumors and control tissues from healthy individuals (page 515, col. 2)(limitations of Claim 13, 15-16, 45). Maruyama teaches 101 prostate cancers and 32 nonmalignant prostate tissues were analyzed. The results demonstrate that GSTP1 and APC were methylated in prostate cancers at 36% and 27% respectively (page 515, col. 2). Table 3 illustrates that the frequency of aberrant methylation in prostate tissues differs significantly between cancers and nonmalignant tissues for both GSTP1 and APC. (page 516). Maruyama studies the tumor state and methylation patterns and both GSTP1 and APC were more frequently methylated in high state (Stage II or IV) as opposed to low stage (Stage I or II) (Figure 2, page 517)(limitations of Claim 37-39, 44). Maruyama specifically concludes that the methylation profile of prostate cancers correlates with clinicopathological features of poor prognosis (page 518, col. 2).

Maruyama does not specifically teach quantifying promoter methylation of CRBP1.

However, Esteller teaches primers for detection of CRBP1 methylation in normal and cancer cell lines. CRBP1 methylation appeared in premalignant lesions and frequently occurred with RARB2 methylation in the same tumors. Esteller teaches that promoter hypermethylation was found in numerous human primary tumors. Table 1 outlines numerous primary tumors that have methylation of CRBP1 promoter.

Therefore, it would have been prima facie obvious at the time the invention was made to have analyzed the promoter methylation of GSTP1, APC, RASSF1A and CRBP1 to analyze a range of cancers. The prior art teaches that GSTP1, APC, RASSF1a are hypermethylated in prostate cancers as taught by Maruyama while CRBP1 is hypermethylated in numerous cancers. Maruyama teaches that using the markers in combination provided even more diagnostic power than using a single marker alone (page 1979, col. 2). Thus, a method for combining the panel of genes taught by Maruyama and Esteller to detecting a neoplasia by detecting the hypermethylation of the promoters of GSTP1, APC, RASSF1A and CRBP1 would have provided additional information and increased the information derived from the analysis to indicate the presence of a neoplasia in the sample.

9. Claims 2, 7, 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maruyama et al. (Clinical Cancer Research, Vol. 8, pages 514-519, February 2002) in view of Esteller et al. (Cancer Research, Vol. 62, pages 5902-5905, October 14, 2002) and further in view of Nakayama et al. (Lab Investigation, Vol. 81, No. 7, pages 1049-1057, 2001).

Maruyama and Esteller do not specifically teach analysis of promoter methylation for RARB2. Moreover, the combination of Maruyama and Esteller do not specifically teach detecting prostate cancer.

However, Nakayama teaches aberrant methylation of **RARB2** was detected in 79% of primary prostate cancers and not in normal prostate samples. Nakayama

Art Unit: 1634

teaches using bisulfite PCR method to detail the methylation status of the RARB2 promoter region status. Table 1 illustrates that RARB2 methylation was found in normal prostate cancer and hormone-refractory prostate cancer (page 1052).

Therefore, it would have been prima facie obvious at the time the invention was made to have analyzed the promoter methylation of GSTP1, APC, RASSF1A, RARB2 and CRBP1 to detect prostate cancer. The prior art specifically teaches GSTP1, APC, RASSF1A, and RARB2 are hypermethylated in prostate cancers. The prior art further teaches that the methylation of **RAR-beta2** and **CRBP1** occurred frequently in the same tumors. CRBP1 methylation appeared in premalignant lesions and frequently occurred with RARB2 methylation in the same tumors. Esteller teaches that promoter hypermethylation was found in numerous human primary tumors. It would have been prima facie obvious to have analyzed the panel of genes known to be hypermethylated in cancers to provide a better analysis of promoter methylation and detection of cancers.

With specific respect to Claims drawn to prostate cancer, the prior art teaches GSTP1, APC, RASSF1A, and RARB2 are hypermethylated in prostate cancers. The prior art further teaches that the methylation of **RAR-beta2** and **CRBP1** occurred frequently in the same tumors. It would have been prima facie obvious to analyze whether CRBP1 is hypermethylated in prostate cancers. The prior art teaches that the two genes are frequently methylated in the same tumors so there is a reasonable expectation of success that **CRBP1** is hypermethylated in prostate cancers, since RAR-beta2 promoter methylation is known to be associated with prostate cancer.

10. Claim 52 is rejected under 35 U.S.C. 103(a) as being unpatentable over Maruyama et al. (Clinical Cancer Research, Vol. 8, pages 514-519, February 2002) in view of Esteller et al. (Cancer Research, Vol. 62, pages 5902-5905, October 14, 2002) in view of Goessl et al. (Cancer Research, Vol. 60, pages 5941-5945, November 2000).

Maruyama teaches analyzing aberrant promoter methylation profiles of prostate cancers. In particular gene promoter methylation was analyzed in 101 prostate cancer samples (limitations of Claim 7). Among the genes analyzed were GSTP1 and APC (abstract)(limitations of Claim 18). Maruyama teaches analyzing prostate specimens using MSP assays (limitations of Claim 51). Maruyama teaches that negative control samples without DNA were included for each set of PCR. Moreover, the conditions for MSP were selected to distinguish between tumors and control tissues from healthy individuals (page 515, col. 2)(limitations of Claim 13, 15-16, 45). Maruyama teaches 101 prostate cancers and 32 nonmalignant prostate tissues were analyzed. The results demonstrate that GSTP1 and APC were methylated in prostate cancers at 36% and 27% respectively (page 515, col. 2). Table 3 illustrates that the frequency of aberrant methylation in prostate tissues differs significantly between cancers and nonmalignant tissues for both GSTP1 and APC. (page 516). Maruyama studies the tumor state and methylation patterns and both GSTP1 and APC were more frequently methylated in high state (Stage II or IV) as opposed to low stage (Stage I or II) (Figure 2, page 517)(limitations of Claim 37-39, 44). Maruyama specifically concludes that the

Art Unit: 1634

methylation profile of prostate cancers correlates with clinicopathological features of poor prognosis (page 518, col. 2).

Esteller teaches primers for detection of CRBP1 methylation in normal and cancer cell lines. CRBP1 methylation appeared in premalignant lesions and frequently occurred with RARB2 methylation in the same tumors. Esteller teaches that promoter hypermethylation was found in numerous human primary tumors. Table 1 outlines numerous primary tumors that have methylation of CRBP1 promoter.

Maruyama nor Esteller specifically teaches that patient samples for analyzing promoter methylation may be serum, plasma, ejaculate or urine.

However, at the time the invention was made, the prior art had analyzed methylation-specific PCR for DNA based detection of prostate cancer in bodily fluids. In particular Goessl teaches analysis of GSTP1, the most frequent DNA alteration in prostatic cancer with MSP in serum, plasma, ejaculate and urine. Maruyama teaches each of these samples demonstrated GSTP1 promoter methylation at detectable levels.

Therefore, at the time the invention was made, it would have been obvious to have modified the method of Maruyama which uses prostate tissues with a method relying on serum, plasma, ejaculate or urine. Goessl teaches that promoter methylation may be detected in serum, plasma, ejaculate and urine. The ordinary artisan would have been motivated to have used these samples instead of prostate tissue because they may be obtained by noninvasive detection means. The analysis of serum, plasma, ejaculate and urine do not require any surgery.

Art Unit: 1634

11. Claims 58-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maruyama et al. (Clinical Cancer Research, Vol. 8, pages 514-519, February 2002) in view of Esteller et al. (Cancer Research, Vol. 62, pages 5902-5905, October 14, 2002).

Maruyama teaches analyzing aberrant promoter methylation profiles of prostate cancers. In particular gene promoter methylation was analyzed in 101 prostate cancer samples (limitations of Claim 7). Among the genes analyzed were GSTP1 and APC (abstract)(limitations of Claim 18). Maruyama teaches analyzing prostate specimens using MSP assays (limitations of Claim 51). Maruyama teaches that negative control samples without DNA were included for each set of PCR. Moreover, the conditions for MSP were selected to distinguish between tumors and control tissues from healthy individuals (page 515, col. 2)(limitations of Claim 13, 15-16, 45). Maruyama teaches 101 prostate cancers and 32 nonmalignant prostate tissues were analyzed. The results demonstrate that GSTP1 and APC were methylated in prostate cancers at 36% and 27% respectively (page 515, col. 2). Table 3 illustrates that the frequency of aberrant methylation in prostate tissues differs significantly between cancers and nonmalignant tissues for both GSTP1 and APC. (page 516). Maruyama studies the tumor state and methylation patterns and both GSTP1 and APC were more frequently methylated in high state (Stage II or IV) as opposed to low stage (Stage I or II) (Figure 2, page 517)(limitations of Claim 37-39, 44). Maruyama specifically concludes that the methylation profile of prostate cancers correlates with clinicopathological features of poor prognosis (page 518, col. 2).

Esteller teaches primers for detection of CRBP1 methylation in normal and cancer cell lines. CRBP1 methylation appeared in premalignant lesions and frequently occurred with RARB2 methylation in the same tumors. Esteller teaches that promoter hypermethylation was found in numerous human primary tumors. Table 1 outlines numerous primary tumors that have methylation of CRBP1 promoter.

Neither Maruyama nor Esteller specifically teach selecting a treatment following quantification of promoter methylation. Maruyama does teach that methylation of GSTP1 and APC are indicative of high stage prostate cancer. The ordinary artisan would have been motivated to have selected a treatment that is appropriate for the high stage predicted. Treatments for high stage prostate cancer are known in the art including chemotherapy and surgery. Thus, it would have been obvious at the time the invention was made to have identified patients with methylation at GSTP1 and APC and selected a treatment for these patients.

Conclusion

12. No claims allowable over the art.

13. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Harden (Clinical Cancer Research, Vol. 9, pages 1370-1375, April 2003) teaches gene promoter hypermethylation in tumors and lymph nodes of stage I lung cancer patients. In particular Harden teaches testing five gene promoters including GSTP1 and APC by real-time methylation-specific PCR in primary tumors from 90 stage

Art Unit: 1634

I lung cancer patients for aberrant DNA methylation (abstract). Harden teaches using real-time QMSP (page 1370, col. 2)(limitations of Claim 15). To teach the relative levels of methylated promoter DNA in each sample, the values of the gene of interest were compared with the values of the internal reference gene to obtain a ratio that was then multiplied by 100 to give a percentage value (page 1371, col. 1)(limitations of Claim 16). Harden teaches that leukocyte DNA from a healthy individual was used as the negative control for all genes (page 1371, col. 2)(limitations of Claim 13). 8% of the primary tumors were methylated at GSTP1 and 72% at APC. Harden further analyzes the presence of tumor methylation as a marker to investigate the presence of occult metastasis in corresponding histologically negative lymph nodes (i.e. prognosis). Table 1 illustrates stage, histology, tumor methylation and lymph node methylation for the 90 stage I NSCLC cases. Harden teaches that APC and GSTP1 correlated with nonsquamous histology (page 1372, col. 1).

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

Art Unit: 1634

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, can be reached on (571)272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

/Jeanine Goldberg/

Primary Examiner

November 25, 2011